

Acute Kidney Injury: Definition, Pathophysiology and Clinical Phenotypes

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Abstract

Acute kidney injury (AKI) is a clinical syndrome that complicates the course and worsens the outcome in a significant number of hospitalised patients. Recent advances in clinical and basic research will help with a more accurate definition of this syndrome and in the elucidation of its pathogenesis. With this knowledge we will be able to conduct more accurate epidemiologic studies in an effort to gain a better understanding of the impact of this syndrome. AKI is a syndrome that rarely has a sole and distinct pathophysiology. Recent evidence, in both basic science and clinical research, is beginning to change our view for AKI from a single organ failure syndrome to a syndrome where the kidney plays an active role in the progress of multi-organ dysfunction. Accurate and prompt recognition of AKI and better understanding of the pathophysiologic mechanisms underlying the various clinical phenotypes are of great importance to research for effective therapeutic interventions. In this review we provide the most recent updates in the definition, epidemiology and pathophysiology of AKI.

Introduction

The concept of Acute Renal Failure (ARF)¹ has undergone significant re-examination in recent years. Traditionally, emphasis was given to the most severe acute reduction in kidney function, as manifested by severe azotaemia and often by oliguria or anuria. However, recent evidence suggests that even relatively mild injury or impairment of kidney function manifested by small changes in serum creatinine (sCr) and/or urine output (UO), is a predictor of serious clinical consequences.²⁻⁵

Acute Kidney Injury (AKI) is the term that has recently replaced the term ARF. AKI is defined as an abrupt (within hours) decrease in kidney function, which encompasses both injury (structural damage) and impairment (loss of function). It is a syndrome that rarely has a sole and distinct pathophysiology. Many patients with AKI have a mixed aetiology where the presence of sepsis, ischaemia and nephrotoxicity often co-exist and complicate recognition and treatment. Furthermore the syndrome is quite common among patients without critical illness and it is essential that health care professionals, particularly those without specialisation in renal disorders, detect it easily.

Classification of AKI includes pre-renal AKI, acute post-renal obstructive nephropathy and intrinsic acute kidney diseases.

Of these, only 'intrinsic' AKI represents true kidney disease, while pre-renal and post-renal AKI are the consequence of extra-renal diseases leading to the decreased glomerular filtration rate (GFR). If these pre- and/or post-renal conditions persist, they will eventually evolve to renal cellular damage and hence intrinsic renal disease.

The current diagnostic approach of AKI is based on an acute decrease of GFR, as reflected by an acute rise in sCr levels and/or a decline in UO over a given time interval.⁶⁻⁸ Recently several biomarkers have been proposed for the diagnosis of AKI and these are in various stages of development and validation.⁹⁻¹² Nevertheless, it is not clear, if a single or multiple biomarker approach is necessary to diagnose the complicated and multifactorial aspects of AKI.¹³⁻¹⁶

However, in addition to the analytical difficulties associated with each specific biomarker, there is also an issue concerning the appropriate reference point, and more specifically about using sCr as the standard, for the clinical evaluation of these biomarkers. It is known that sCr is insensitive to acute changes of renal function and levels can vary widely with age, gender, muscle mass, diet, medications and hydration status. Moreover it is not a direct marker of tubular damage, but rather a marker of GFR, and substantial increases in sCr can be observed in renal hypo-perfusion even when the kidneys are

structurally intact, resulting in pre-renal azotaemia. For these reasons sCr is considered an ‘imperfect gold standard’ for the diagnosis of AKI.¹⁷ Another issue with sCr is that in most clinical situations its true baseline value is not known, which makes the evaluation of patients very difficult.¹⁸⁻²⁰ Moreover, given the phenotypic variability of AKI (different clinical phenotypes with distinct underlying pathophysiologies), it is not clear whether different approaches are necessary for diagnosis and monitoring of the clinical course and therapy.

In this review we will discuss the epidemiology and the definition of AKI. We will also discuss the clinical phenotypes, their pathophysiology and the link between AKI and remote organ dysfunction.

History

The first description of ARF, then termed *ischuria renalis*, was by William Heberden in 1802.²¹ At the beginning of the twentieth century, ARF, then named *Acute Bright's disease*, was described in William Osler's Textbook for Medicine (1909), to be “as a consequence of toxic agents, pregnancy, burns, trauma or operations on the kidneys”. During the First World War the syndrome was named *war nephritis*,²² and was reported in several publications. The syndrome was forgotten until the Second World War, when Bywaters and Beall published their classical paper on *crush syndrome*.²³ Acute tubular necrosis (ATN) was the term that was used to describe this clinical entity, because of histological evidence for patchy necrosis of renal tubules at autopsy. For many years in clinical practice, the terms ATN and ARF were used interchangeably. However, it is Homer W. Smith who is credited for the introduction of the term *acute renal failure*, in a chapter on *Acute renal failure related to traumatic injuries* in his 1951 textbook *The kidney-structure and Function in Health and Disease*. Until recently, a precise biochemical definition for ARF was missing. As a consequence there was no consensus on the diagnostic criteria, resulting in multiple different definitions. A 2002 survey revealed at least 35 definitions in the scientific literature.²⁴

Epidemiology

The lack of standard definition of the syndrome had a great impact in the reported incidence and clinical significance of AKI and its true impact is not well known. The incidence varies, depending on the definition used, patient population and geographical area studied.²⁵⁻²⁷

Large differences are observed in the incidence and the causes of AKI between developing and developed countries. A recent review described the similarities and differences in incidence, cause, pathophysiology, and public health implications of AKI in developed and developing regions of the world.²⁸

In urban areas of developing countries, main causes of AKI are hospital acquired (renal ischaemia, sepsis and nephrotoxic drugs) while in rural areas it is more commonly a consequence of community acquired disease (diarrhoea, dehydration, infectious diseases, animal venoms etc.). Under-reporting of AKI especially in developing countries is also a major problem that relates with the true knowledge of its impact in many parts of the world.²⁹

In developed countries the prevalence of AKI is increasing. In *hospital inpatients* it is estimated to occur up to 15% and is more common in *critically ill* patients, in whom its prevalence is estimated to be up to 60%.^{28,30-34} On the other hand *community* AKI is usually uncommon although a recent study estimated its incidence at 4.3% among all hospital admissions.³⁵ However even this incidence remains an underestimate of the true impact of community acquired AKI due to non-referral of patients to hospitals.

Although several studies have focused on special populations (the elderly and children), large epidemiologic studies with children are missing and the incidence of paediatric AKI is inadequately described. The reason is that most paediatric epidemiologic studies were limited to a single centre with small number of patients and focused on critical care populations or on children requiring dialysis.³⁶⁻⁴⁰ In a recent large scale epidemiologic study, the incidence of AKI in hospitalised children in the US was found to occur in 3.9 per 1000 admissions.³⁶ The majority of AKI cases in children are secondary to volume responsive mechanisms (e.g. diarrhoea, renal hypoperfusion after surgery) and secondary to sepsis.⁴¹ Other conditions such as uraemic haemolytic syndrome and glomerulonephritis have been shown to be of increased frequency in different parts of the world with varied outcomes usually due to late referral of children to hospitals.

Multiple studies have shown that AKI in the elderly (usually defined as older than 65 years) is increasingly common and that there is an age-dependent relationship between AKI and older age.^{42,43} This has been attributed in part to anatomic and physiologic changes in the ageing kidney and in part to various comorbidities - i.e. hypertension, cardiovascular disease, chronic kidney disease (CKD) - that may require procedures and/or medications that act as kidney stressors and alter renal haemodynamics or are nephrotoxic.⁴⁴⁻⁴⁶

Several studies have also shown that AKI is associated with short and long term adverse outcomes. These have been reviewed recently.⁴⁷⁻⁴⁹ Ricci et al., in a systematic review of 24 studies that involved more than 71000 patients where the RIFLE criteria (see Table 1 for terminology and definition) were used for AKI definition and staging found that the

mortality rate was 18.9% in the 'risk' class, 36.1% in 'injury' class and 46.5% in 'failure' class. In non-AKI patients the mortality was 6.9%. Among AKI patients the relative risk for death (with respect to non-AKI patients) was 2.40 for 'risk' class, 4.15 for 'injury' class and 6.15 for 'failure class'.⁵⁰ In intensive care unit (ICU) populations, observational studies have shown that 4-5% of all critically ill patients develop severe AKI requiring renal replacement therapy (RRT) with the mortality rate often exceeding 60%.^{31,51,52}

Although mortality and development of CKD are reported with increased rates in these studies their incidence is quite variable. The factors that associate with long-term prognosis (especially with CKD progression) are poorly understood. Pre-AKI baseline renal function must be known and post-AKI recovery must be clearly defined in order to determine such outcomes. The first is often missing or is guessed in many studies and the second lacks a standard definition.^{47,53,54}

Terminology and definitions

The term Acute Kidney Injury (AKI) was used for the first time by William MacNider in 1918 in a situation of acute mercury poisoning, but became the preferred term in 2004 when ARF was redefined with the now widely accepted consensus criteria known as RIFLE (an acronym of the Risk-Injury-Failure-Loss-End stage kidney disease).^{6,55}

Principal tools to detect AKI were consecutive measurements of sCr, serum urea (sUr), urinalysis, and measurements of UO. Urine indices such as fractional excretion of sodium (FeNa) and urea (FeUr) were also used to differentiate transient from persistent AKI. Agreement in diagnostic criteria for AKI came later from multiple consensus groups. First was the *Acute Dialysis Quality Initiative (ADQI) group*. In 2002 they developed a system for diagnosis and classification of *acute impairment of kidney function* through a broad consensus of experts, resulting in the RIFLE criteria. The characteristics of this diagnostic system are summarised in Table 1. With this system three severity grades are defined (Risk, Injury and Failure) and two outcome classes (Loss and End-Stage Renal Disease (ESRD)). The severity criteria of AKI are defined on the basis of the changes in sCr or UO where the worst of each criterion is used. The outcome criteria are defined by the duration of impairment of kidney function.⁶

The importance of RIFLE criteria is that they move beyond ARF. The term "*acute kidney injury/impairment*" has been proposed to encompass the "*entire spectrum of the syndrome from minor changes in markers of renal function to requirement for renal replacement therapy (RRT)*". Therefore the concept of AKI, as defined by RIFLE, creates a new paradigm. AKI encompasses ATN and ARF as well as other, less severe conditions. It includes patients without actual damage to the

Table 1. RIFLE criteria for classification and staging AKI and the modifications proposed by the AKIN network - modified from references (6 and 7)

RIFLE criteria for classification/staging AKI			AKIN criteria for classification/staging AKI		
Stage	GFR criteria	Urine output criteria	Stage	Serum Creatinine criteria	Urine output criteria
Risk	1.5fold increase in sCr or >25% decrease in GFR	UO < 0.5mL/kg/h for 6h	Stage 1	Absolute increase in sCr \geq 0.3 mg/dL (\geq 26.5 μ mol/L) or \geq 1.5 to 2.0 fold from baseline	UO < 0.5mL/kg/h for 6h
Injury	2.0fold increase in sCr or >50% decrease in GFR	UO < 0.5mL/kg/h for 12h	Stage 2	Increase in sCr > 2.0 to 3.0 fold from baseline	UO < 0.5mL/kg/h for 12h
Failure	3.0fold increase in sCr or >75% decrease in GFR or sCr >4.0 mg/dL with an acute increase of 0.5 mg/dL	UO < 0.3mL/kg/h for 24h or anuria for 12 h	Stage 3	Increase in sCr > 3fold from baseline or increase of sCr to \geq 4.0 mg/dL (\geq 354 μ mol/L) with an acute increase of at least 0.5 mg/dL (44 μ mol/L)	UO < 0.3mL/kg/h for 24h or anuria for 12h
Loss	Complete loss of kidney function for > 4 weeks				
ESKD	End stage kidney disease for > 3 months				

ESKD=end stage kidney disease, AKI=acute kidney injury, GFR=glomerular filtration rate, sCr= serum creatinine, UO=urinary output

kidney but with functional impairment relative to physiologic demand. Including such patients in the classification of AKI is conceptually attractive because these are precisely the patients that may benefit from early intervention. The RIFLE criteria have also been modified for use in the paediatric setting.⁵⁶ Nevertheless the RIFLE definition is not free of ambiguities. Pickering et al⁵⁷ showed that there was a mismatch between increases in sCr concentration and decreases in GFR (estimated with MDRD or Cockcroft-Gault formulae) in the descriptions of Risk and Failure severity grades. A 1.5-fold increase in sCr corresponds to a one-third decrease (not 25%) in GFR and a three-fold increase corresponds to a two-third decrease in GFR (not 75%). If the GFR is not directly measured but estimated by a formula then results might be also different depending on the formula used. With the MDRD formula a 1.5-fold increase in sCr corresponds to a 37% decrease in GFR, and a three-fold increase in sCr to a 72% decrease in GFR.⁵⁷

In 2007, the Acute Kidney Injury Network (AKIN) group proposed a modified version of the RIFLE criteria, which aimed to improve the sensitivity of AKI diagnostic criteria.⁷ There were several changes: an absolute increase in sCr of at least 0.3 mg/dL (26.5 µmol/L) was added to stage 1; the GFR criterion was removed; patients starting RRT were classified as stage 3, irrespectively of sCr values; and outcome classes were removed. The characteristics of this system are summarised in Table 1.

Only one criterion (sCr or UO) has to be fulfilled in order to qualify for a stage. Time becomes more important for AKI diagnosis in the AKIN definition: *changes between two sCr*

values within a 48-hour period are required, while one week was proposed by the ADQI group in the original RIFLE criteria. Severity of AKI in AKIN is staged over the course of 7 days by the fold-change in sCr from baseline.

The latest classification of AKI proposed by the Acute Kidney Injury Working Group of KDIGO (Kidney Disease: Improving Global Outcomes), is based on the previous two classifications, and had the aim of unifying the definition of AKI.⁸ By the KDIGO definition, AKI is diagnosed by an absolute increase in sCr, at least 0.3 mg/dL (26.5 µmol/L) within 48 hours or by a 50% increase in sCr from baseline within 7 days, or a urine volume of less than 0.5 mL/kg/h for at least 6 hours (Table 2).

A patient's progress *can be staged over the entire time frame encompassed by an episode of AKI*. An increase in sCr up to 3 times from baseline, or a sCr of more than 4.0 mg/dL (354 µmol/L) or initiation of RRT, are all classified as stage 3. KDIGO removes the 0.5 mg/dL increase for sCr >4 mg/dL to diagnose stage 3. KDIGO explicitly states that a *rolling baseline* can be used over 48-hour and 7-day periods for diagnosis of AKI, while in RIFLE or AKIN it is not clear how this is handled. Changes were also made to severity stage 3 to enable incorporation of paediatric population into both definition and staging.

Aetiology of AKI

There are numerous potential causes of AKI, mainly related to a focal mismatch between oxygen and nutrient delivery (because of impaired microcirculation) to the nephrons and

Table 2. AKI definition and staging according to KDIGO criteria - modified from reference (8)

AKI is <i>defined</i> as any of the following:		
1	Increase in sCr ≥ 0.3 mg/dL (≥ 26.5 µmol/L) within 48 hours; or	
2	Increase in sCr ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or	
3	Urine volume < 0.5 mL/kg/h for 6 hours.	
AKI is <i>staged for severity</i> according to the following criteria		
Stage 1	1.5–1.9 times baseline OR ≥ 0.3 mg/dL (≥ 26.5 µmol/L) absolute increase in sCr	Urine volume < 0.5 mL/kg/h for 6–12 hours
Stage 2	sCr ≥ 2.0 –2.9 times baseline	Urine volume < 0.5 mL/kg/h for ≥ 12 hours
Stage 3	sCr ≥ 3.0 times from baseline OR Increase in sCr to ≥ 4.0 mg/dL (≥ 353.6 µmol/L) OR Initiation of renal replacement therapy OR, In patients < 18 years, decrease in eGFR to < 35 mL/min per 1.73 m^2	Urine volume < 0.3 mL/kg/h for ≥ 24 hours OR Anuria for ≥ 12 hours

sCr=serum creatinine, eGFR= estimated glomerular filtration rate

increased energy demands (due to cellular stress).⁵⁸ For many years the diagnosis and management of AKI was based on the concept of classification to three main categories: pre-renal, intrinsic and post-renal (Figure 1).⁵⁹⁻⁶¹

In **Pre-renal AKI**, renal hypoperfusion leads to a decreased GFR (without damage to the renal parenchyma), as an adaptive response to various extra-renal insults.⁶² It is known that maintaining a normal GFR is dependent on adequate renal perfusion. The kidneys receive up to 25% of cardiac output and thus any failure of the systematic circulating blood volume or isolated failure of the intra-renal circulation can have a profound impact on renal perfusion (Table 3).

Post-renal AKI occurs after acute obstruction of the urinary flow, which increases intra-tubular pressure and thus decreases GFR.⁶³ In addition, acute urinary tract obstruction can lead to impaired renal blood flow and inflammatory processes that also contribute to diminished GFR.⁶⁴ Post-renal AKI can develop if the obstruction is located at any level within the urinary collection system (from the renal tubule to urethra). In case the obstruction is above the bladder it must involve both kidneys (or one kidney in the case of a patient with a single functioning kidney) to produce significant renal failure.⁶⁵ However, a patient with pre-existing renal insufficiency may develop AKI with obstruction of only one kidney. Urinary obstruction may present as anuria or intermittent urine flow (such as polyuria alternating with oliguria) but may also present as nocturia or nonoliguric AKI (Table 3). Timely reversion of pre-renal or post-renal causes usually results in prompt recovery of function, but late correction can lead to kidney damage.

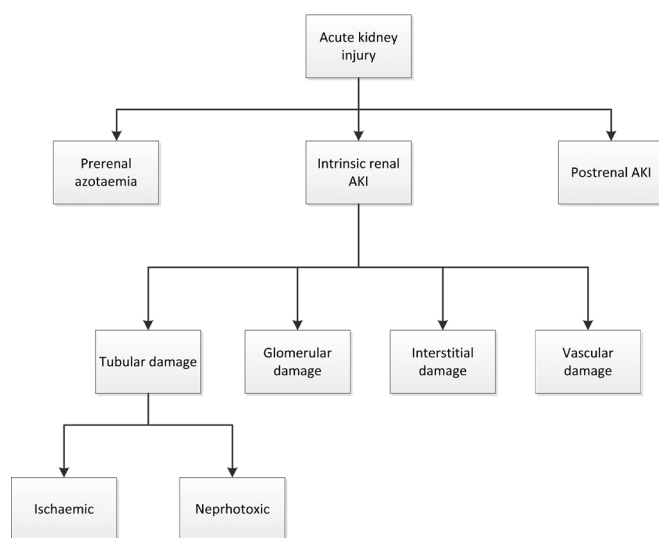


Figure 1. Aetiologies of acute kidney injury

Intrinsic renal aetiologies of AKI can be challenging to evaluate because of the wide variety of injuries that can occur to the kidney. Generally, four structures of the kidney are involved including **tubules, glomeruli, the interstitium, and intra-renal blood vessels**. (Figure 1 and Table 3)

Acute tubular necrosis (ATN) is the term used to designate AKI resulting from damage to the tubules. It is the most common type of intrinsic kidney injury. AKI from glomerular damage occurs in severe cases of acute glomerulonephritis (GN). AKI from vascular damage occurs because injury to intra-renal vessels decreases renal perfusion and diminishes GFR and finally acute interstitial nephritis occurs due to an allergic reaction to a variety medications or an infection.

The different clinical phenotypes of AKI and their pathophysiology

Essentially AKI is a term used to describe the clinical syndrome that occurs when renal function is acutely decreased to a point that the body accumulates waste products and becomes unable to maintain electrolyte, acid-base and water balance.⁵⁸

The pathophysiology of AKI is multifactorial and complex. The most common cause of AKI is ischaemia, which can occur for a number of reasons (Table 3). Physiological adaptations, in response to the reduction in blood flow can compensate to a certain degree, but when delivery of oxygen and metabolic substrates becomes inadequate, the resulting cellular injury leads to organ dysfunction. The kidney is highly susceptible to injury related to ischaemia, resulting in vasoconstriction, endothelial injury, and activation inflammatory processes.⁶⁶ This susceptibility can be explained in part from structural associations between renal tubules and blood vessels in the outer medulla of the kidney, with ischaemia compromising blood flow to critical nephron structures present therein. Following the reduction in effective kidney perfusion, the epithelial cells are unable to maintain adequate intracellular ATP for essential processes. This ATP-depletion leads to cell injury and if it is severe enough can lead to cell death by necrosis or apoptosis. During an ischaemic insult all segments of the nephrons can be affected but proximal tubular cells are the most commonly injured. In addition, the nephron's natural function is to filter, concentrate and reabsorb many substances from tubular lumen, and the concentration of these substances may reach toxic levels for the surrounding epithelial cells. A detailed description of the sequence of events and the cellular changes during ischaemic AKI can be found elsewhere.⁶⁷⁻⁶⁹

AKI is also very common in the setting of sepsis. In sepsis the circulation is hyperdynamic and blood flow is altered, albeit not necessarily in the ischaemic range, and GFR drops rapidly.⁷⁰ The pathophysiology of septic-AKI is very complex

Table 3. Causes of acute kidney injury.

Category	Abnormality	Possible causes
Prerenal	Hypovolaemia	Haemorrhage Volume depletion Renal fluid loss (over-diuresis) Third space (burns, peritonitis, muscle trauma)
	Impaired cardiac function	Congestive heart failure Acute myocardial infarction Massive pulmonary embolism
	Systemic vasodilatation	Anti-hypertensive medications Gram negative bacteraemia Cirrhosis Anaphylaxis
	Increased vascular resistance	Anaesthesia Surgery Hepatorenal syndrome NSAID medications Drugs that cause renal vasoconstriction (i.e. cyclosporine)
Intrinsic	Tubular	Renal ischaemia (<i>shock, complications of surgery, haemorrhage, trauma, bacteraemia, pancreatitis, pregnancy</i>) Nephrotoxic drugs (<i>antibiotics, antineoplastic drugs, contrast media, organic solvents, anaesthetic drugs, heavy metals</i>) Endogenous toxins (<i>myoglobin, haemoglobin, uric acid</i>)
	Glomerular	Acute post-infectious glomerulonephritis Lupus nephritis IgA glomerulonephritis Infective endocarditis Goodpasture syndrome Wegener disease
	Interstitium	Infections (<i>bacterial, viral</i>) Medications (<i>antibiotics, diuretics, NSAIDs, and many more drugs</i>)
	Vascular	Large vessels (<i>bilateral renal artery stenosis, bilateral renal vein thrombosis</i>) Small vessels (<i>vasculitis, malignant hypertension, atherosclerotic or thrombotic emboli, haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura</i>)
Postrenal	Extrarenal obstruction	Prostate hypertrophy Improperly placed catheter Bladder, prostate or cervical cancer Retroperitoneal fibrosis
	Intrarenal obstruction	Nephrolithiasis Blood clots Papillary necrosis

NSAID=non-steroid anti-inflammatory drug

and involves inflammation, oxidative stress microvascular dysfunction and amplification of injury via secretion of cytokines by tubular cells.⁷¹ The traditional classification of AKI into pre-renal, intrinsic-renal and post-renal has recently been challenged since histological diagnosis is performed very rarely and distinction between pre-renal azotaemia and tubular damage cannot be confirmed and only hypothesised retrospectively. Our knowledge is mainly obtained from animal studies where the ischaemia-reperfusion model has been extensively studied. Other models (toxic injury, septic model) are less studied.⁷² However, these latter models are quite extreme and are not representative of the clinical manifestations of AKI in humans, where renal blood flow never fully stops (except in certain surgical procedures i.e. abdominal aortic aneurysm repair) but less severe forms of low blood flow followed by reperfusion generally occur. Controversy also exists regarding the extent of damage as well as the cell types affected by this damage (proximal vs distal tubular cells).⁷³ The animals used in the studies are usually young and healthy but most patients developing AKI are old and with significant comorbidities (diabetes, CKD, hypertension). Moreover in experimental animals AKI is mono-causal while in humans is often of multiple co-existing aetiologies. A further analysis of pathophysiologic mechanisms is beyond the scope of this review. The reader can refer to several excellent reviews analysing pathophysiologic mechanisms in AKI.^{44,58,63,66,68,69,71,74-77}

Special clinical scenarios

Rhabdomyolysis

Rhabdomyolysis is a syndrome that is characterised by the breakdown and necrosis of damaged skeletal muscle and subsequent release of its contents (i.e. myoglobin, sarcoplasmic proteins) into extracellular fluid and circulation.⁷⁸⁻⁸⁰ These products may be filtered through the glomeruli, leading to AKI via different mechanisms, such as intratubular obstruction secondary to protein precipitation, renal vasoconstriction, inflammation and tubular damage associated with reactive oxygen species production. Rhabdomyolysis usually develops in the setting of one or more of the following situations: disruption of the substrates and/or oxygen for metabolism (i.e. ischaemia, hypoxia, crush injuries), excessive metabolic demand (i.e. strenuous exercise), impaired cellular energy production (i.e. hereditary enzymatic disorders, toxins), and/or increased intracellular calcium influx.^{81,82}

The clinical presentation of this multifactorial and multicausal syndrome varies from an asymptomatic but detectable elevations of CK and myoglobin in blood to a life threatening condition with fulminant AKI. The ability to predict rhabdomyolysis induced AKI is critical since it is one of the leading causes of AKI. Rhabdomyolysis contributes to 5-25%

of all AKI cases and 10-50% of patients with some degree of rhabdomyolysis develop AKI.⁸²

Drug-induced AKI

Medications frequently show toxic effects on the kidney as glomerular, interstitial and tubular cells encounter significant concentrations of medications and their metabolites, which can induce changes in kidney function and structure. Renal tubular cells are particularly vulnerable to the toxic effects of drugs because of their role in concentrating and reabsorbing glomerular filtrate, which exposes them to high levels of circulating toxins. Renal toxicity can be a result of haemodynamic changes, direct injury to cells and tissue, inflammatory tissue injury and obstruction of renal excretion. The true incidence of drug-induced nephrotoxicity is difficult to determine. Subtle renal damage (i.e. acid-base abnormalities, disorders of water balance, electrolyte imbalances) and mild urinary sediment abnormalities associated with commonly used medications are frequently unrecognised and the detection is often delayed until an overt change in renal function is apparent, usually by an increase in sCr. Three recent reviews explore in detail the mechanisms underlying renal injury related to the use of most common drugs used in clinical practice.⁸³⁻⁸⁵

Contrast Induced Acute Kidney Injury (CI-AKI)

Contrast induced AKI (CI-AKI) previously known as contrast induced nephropathy (CIN) is a syndrome in which acute renal dysfunction is diagnosed following intravascular administration of contrast agents. Contrast agents are used widely for diagnostic and therapeutic purposes. Their nephrotoxic potential was first suggested at least 50 years ago and today are considered one of the most common causes of AKI among hospitalised patients.^{86,87} The risk of CIN has long been assumed to be proportional to the degree of pre-existing renal dysfunction and it is associated with extended length of hospital stay, accelerated onset of end stage renal disease, need for dialysis, increased mortality and increased costs.^{86,88-90} Although in the past many different definitions were used to define CI-AKI, the new KDIGO definition of AKI applies to CI-AKI and will help us to use a common language in research and in clinical diagnosis of this syndrome. The pathophysiology of CI-AKI is not very well defined. Animal models of CI-AKI suggest several potential mechanisms of nephrotoxicity, including renal ischaemia, vasoconstriction, formation of reactive oxygen species and direct tubular toxicity, which lead to decreased renal perfusion.⁹¹⁻⁹⁴ However, the physiologic relevance of these models may be limited since multiple renal insults are required to express the desired phenotype and such injury is not typically seen in human patients. The causal association between contrast media and nephrotoxicity has been established from several

studies. However the non-existence of a uniform definition and poorly designed studies may have led to overestimation of the frequency and severity of CI-AKI.⁹⁵⁻⁹⁸

Acute kidney injury and extra-renal organ dysfunction

Recent evidence in both basic science and clinical research are beginning to change our view for AKI from a *single organ failure syndrome*, to a *syndrome where the kidney plays an active role in the evolution of multi-organ dysfunction*. Recent clinical evidence suggests that AKI is not only an indicator for severity of illness, but also leads to earlier onset of multi-organ dysfunction with significant effects on mortality. Animal models of renal injury have been used extensively in order to elucidate the mechanism of remote organ dysfunction after AKI despite their limitations due to interspecies differences. These studies have shown a direct effect of AKI on distant organs.⁹⁹⁻¹⁰² These animal studies include models of ischaemia-reperfusion injury and sepsis, mainly lipopolysaccharide endotoxin induced sepsis due to its reproducibility in creating distant organ failure.¹⁰³ AKI is not an isolated event and it results in remote organ dysfunction to the lungs, heart, liver, intestines and brain through a pro-inflammatory mechanism that involves neutrophil cell migration, cytokine expression and increased oxidative stress (Figure 2). Three recent excellent reviews explore the mechanisms and the long-term consequences of AKI other organ systems.¹⁰⁴⁻¹⁰⁶

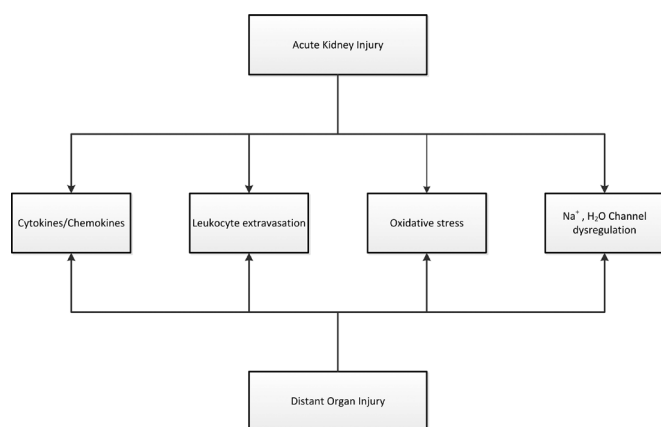


Figure 2. Proposed mechanism of distal organ injury. AKI leads to distant organ injury through a combination of pro-inflammatory and oxidative stress-mediated mechanisms. Serum and distal organ cytokine levels (IL1, IL6, IL10 and TNFα) increase in conjunction with Leukocyte trafficking (neutrophil, lymphocyte and macrophage) and increased oxidative stress (superoxide dismutase, malondialdehyde, and glutathione depletion). In addition, sodium and water channel dysregulation in the lungs aggravate pulmonary edema. - adapted from ref (105).

Kidney-lung crosstalk in the critically ill patient

The kidney and the lung are the two most commonly involved organs in multi-organ failure. Acute lung injury (ALI) and AKI are common complications of sepsis and the development of either increases mortality.^{107,108} Currently there is growing interest in the potential cross-talk that exists between these organs when injured, with one organ causing or contributing to injury to the other. Animal studies have shown that AKI can cause ALI and vice versa. The mechanism of AKI associated lung injury remains incompletely understood. Several studies have shown the involvement of pro-inflammatory and pro-apoptotic factors (leukocyte trafficking, cytokines activation of caspases, oxidative stress and uraemic toxins). AKI leads to lung injury and inflammation and ALI in turn facilitates and exacerbates kidney dysfunction via metabolic and biochemical derangements (Figure 3).¹⁰⁹

Heart-kidney crosstalk: the cardiorenal syndrome

Kidney and cardiac disease are not only common but often co-exist. Both acute and chronic cardiac disease can contribute directly to acute and/or chronic worsening of renal function and vice versa.¹¹⁰ The term cardiorenal syndrome (CRS) is often used to describe this condition and represents an important model for the exploration of the pathophysiology of cardiac and renal dysfunction. Recently a consensus definition/classification scheme has been proposed for the CRS.¹¹¹⁻¹¹³ According to this definition, five subtypes of the CRS exist. Each subtype's etymology reflects the primary and secondary pathology, cardiac and renal as well as dysfunction secondary to systemic disease. (Table 4)

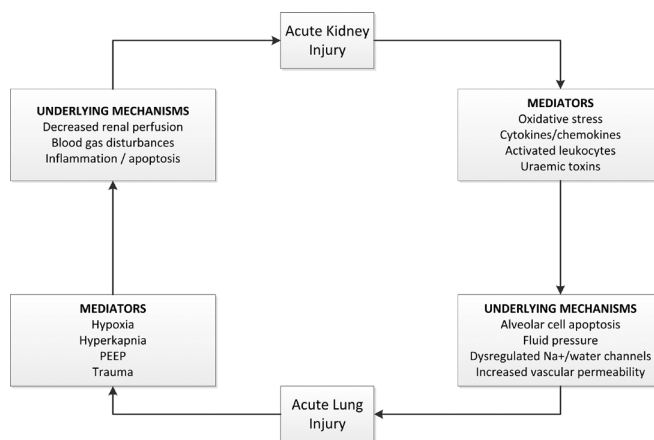


Figure 3. Kidney-lung interactions. AKI induces pathologic effects on the lung via cellular and soluble mediators. ALI in turn facilitates and exacerbates Kidney injury via metabolic and biochemical derangements. - adapted from ref (108).

Kidney-liver interactions: Hepatorenal syndrome

Here it is important to distinguish hepatic dysfunction as a result of AKI as distinct from the well-recognised hepatorenal syndrome (HRS). Liver injury often correlates with severity of kidney injury. Ischaemic AKI induces oxidative stress and promotes inflammation apoptosis and tissue damage to hepatocytes.^{109,114} A recent review examines in detail the experimental evidence for hepatic dysfunction as a consequence of AKI.¹¹⁵

On the other hand the concept of HRS is very well recognised; it is a reversible functional renal impairment that occurs in patients with advanced liver cirrhosis or in patients with fulminant hepatic failure.¹¹⁶⁻¹²⁰ It is characterised by a marked decrease in GFR and renal blood flow in the absence of other causes of renal injury. HRS is not uncommon and occurs in approximately 40% of patients with advanced cirrhosis.¹²¹ Two forms of HRS have been described.^{122,123}

Type 1, is characterised by a rapid and progressive impairment of renal function which is defined by a two-fold increase of sCr to a level $>220 \mu\text{mol/L}$ ($>2.5 \text{ mg/dL}$) in a period of less than two weeks. Type 2, is a less severe form of HRS, characterised by a stable or slowly progressive impairment of

renal function over weeks or months and with a sCr >133 and up to $226 \mu\text{mol/L}$ (or >1.5 and up to 2.5 mg/dL).

The diagnostic criteria require cirrhosis with ascites, a sCr $>133 \mu\text{mol/L}$ (1.5 mg/dL), no improvement in sCr after >2 day upon of withdrawal of diuretics and volume expansion with albumin, absence of shock, no current treatment with nephrotoxic drugs, absence of parenchymal injury as indicated by proteinuria haematuria and/or abnormal ultrasonography.¹²²

These diagnostic criteria present several shortcomings. The sCr should be interpreted with caution in patients with cirrhosis. Reduced endogenous creatinine production which is related to decreased hepatic synthesis and decreased muscle mass from malnutrition, medication-related increases in tubular secretion of creatinine, fluctuations in sCr levels in patients with cirrhosis and large volume ascites and laboratory method dependencies in interference from bilirubin are some of the causes of low sCr values in these patients. Therefore sCr based measurements pose the risk to overestimate renal function and underestimate the severity of renal damage.¹²⁴⁻¹²⁶

Moreover the single cut-off value of a serum creatinine level of $133 \mu\text{mol/L}$ (1.5 mg/dL) may limit treatment to

Table 4. Cardiorenal syndrome classification system – adapted from reference (111)

Classification	Abbreviation	Characteristic	Primary Event	Secondary Event	Criteria for primary/secondary Events
Acute cardio-renal syndrome	CRS type1	Abrupt worsening of cardiac function leading to AKI	AHF, ACS cardiogenic shock	AKI	ESC,AHA,ACC/RIFLE-AKIN
Chronic cardio-renal syndrome	CRS type2	Chronic worsening of cardiac function leading to progressive and permanent chronic kidney disease	CHD	CKD	ESC,AHA,ACC/KDOQI
Acute reno-cardiac syndrome	CRS type3	AKI causing acute cardiac dysfunction	AKI	AHF, ACS arrhythmias shock	RIFLE-AKIN/ ESC,AHA,ACC
Chronic reno-cardiac syndrome	CRS type4	CKD leading to impairment of cardiac function and/or increased risk of adverse cardiovascular events	CKD	CHD, AHF ACS	KDOQI/ ESC,AHA,ACC
Secondary cardio-renal syndrome	CRS type5	Systemic disorders causing both cardiac and renal dysfunction (i.e. septic shock, vasculitis)	Systemic disease (i.e. sepsis)	AKI, CKD AHF, CHD ACS	Disease specific criteria/ RIFLE-AKIN, ESC, AHA, ACC,KDOQI

AKI= acute kidney injury, CKD=chronic kidney disease, ACS= acute coronary syndrome, AHF=acute heart failure, CHD=chronic heart disease,

Table 5. Proposed diagnostic criteria of kidney dysfunction in cirrhosis - adapted from reference (126)

Diagnosis	Definition
Acute kidney injury	Rise in serum creatinine of $\geq 50\%$ from baseline or a rise of serum creatinine by $\geq 26.5 \mu\text{mol/L}$ ($\geq 0.3 \text{ mg/dL}$) in $<48 \text{ h}$ HRS type 1 is a specific form of acute kidney injury
Chronic kidney disease	Glomerular filtration rate of $<60 \text{ ml/min}$ for >3 months calculated using MDRD6 formula HRS type 2 is a specific form of chronic kidney disease
Acute-on-chronic kidney disease	Rise in serum creatinine of $\geq 50\%$ from baseline or a rise of serum creatinine by $\geq 26.5 \mu\text{mol/L}$ ($\geq 0.3 \text{ mg/dL}$) in $<48 \text{ h}$ in a patient with cirrhosis whose glomerular filtration rate is $<60 \text{ ml/min}$ for >3 months calculated using MDRD6 formula

- Both the acute deterioration in renal function and the background chronic renal dysfunction can be functional or structural in nature.
- MDRD6=Modification of Diet in Renal Disease formula calculated using six variables of serum creatinine, age, gender, albumin, blood urea nitrogen and whether or not the patient is African-American

patients with the most severe degree of renal dysfunction. The changes that lead to the development of HRS are not an ‘all-or-none’ phenomenon, but evolve progressively with the natural history of cirrhosis. It is unclear whether patients who have milder degrees of renal dysfunction will also experience adverse outcomes.

As AKI has not been formally defined in patients with cirrhosis, the ADQI and the International Ascites Club (IAC) formed a Working Group in March 2010 and proposed a revised definition of renal dysfunction (both acute and chronic) in patients with cirrhosis.¹²⁷ With this definition Type 1 HRS can be regarded as a specific form of AKI, and Type 2 as a specific form of CKD and the concept of ‘acute-on-chronic’ was introduced (Table 5).

Conclusion

AKI is an important clinical syndrome associated with poor clinical outcomes for hospitalised patients. Considerable advances have been made in refining the definition of this syndrome and in the elucidation of the underlying pathophysiologic mechanisms of the different clinical phenotypes. It is obvious that all clinical phenotypes of AKI cannot fit into a single pathophysiologic pathway. AKI facilitates organ cross-talk and distant organ injury. These innovations will aid in the design of epidemiologic studies and randomised trials of preventive and therapeutic interventions.

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